II. Rejection of Claim 7 Under 35 U.S.C. § 112, First Paragraph

The Action rejects claim 7 under 35 U.S.C. § 112, first paragraph, as allegedly not enabled for the full scope of the claim. Applicants respectfully traverse.

The Examiner states that claim 7 has been "interpreted ... as reading on isolated host cells, *as well as* host cells in the context of a multicellular, transgenic organism and host cells intended for gene therapy" (the Action at page 2, emphasis in original), and notes that "(t)he Specification specifically excludes humans in its discussions of transgenic animals" (the Action at page 4). Applicants agree with the Examiner that claim 7 reads on both isolated host cells and host cells within multicellular organisms, which includes non-human transgenic animals and animals receiving gene therapy. However, despite the **numerous** examples cited by Applicants in the Response filed on February 15, 2005 ("the Response to the Second Action") to the Second Official Action on the merits in the present case, which was mailed on November 17, 2004 ("the Second Action"), of non-human transgenic animals and gene therapy applications that were well-known to the skilled artisan prior to the filing date of the instant application, the Examiner maintains that "(t)he skilled artisan must resort to trial and error experimentation to generate transgenic animals" (the Action at page 4), and that "gene therapy remains unpredictable" (the Action at page 7). Applicants respectfully maintain that the Examiner continues to apply an improper standard of enablement with regard to claim 7, and that under the proper standard, claim 7 fully complies with the enablement requirement of 35 U.S.C. § 112, first paragraph.

With regard to any invention, 35 U.S.C. § 112, first paragraph, requires that the specification "enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to **make** and **use**" the invention (35 U.S.C. § 112, first paragraph, emphasis added). It is well established that the enablement requirement is met if **any** use of the invention (or in this case, certain aspects of the invention) is provided (*In re Nelson*, 126 USPQ 242 (CCPA 1960); *Cross v. Iizuka*, 224 USPQ 739 (Fed. Cir. 1985)). "The enablement requirement is met if the description enables any mode of making and using the invention." *Johns Hopkins Univ. v. CellPro, Inc.*, 47 USPQ2d 1705, 1719 (Fed. Cir. 1998), citing *Engel Indus., Inc. v. Lockformer Co.*, 20 USPQ2d 1300, 1304 (Fed. Cir. 1991). Furthermore, a specification "need describe the invention only in such detail as to enable a person skilled in the most relevant art to make and use it" (*In re Naquin*, 158 USPQ 317, 319 (CCPA 1968), emphasis added).

In the context of non-human transgenic animals, Applicants pointed out in the Response to the

Second Action that there are **hundreds** of examples of non-human transgenic animals, including the non-human transgenic animals listed in the specification as originally filed (worms (nematodes), mice, rats, rabbits, guinea pigs, pigs, birds (chickens), goats and monkeys; see the specification as originally filed at page 17, lines 7-10), years and sometimes decades prior to the filing date of the present application. Applicants further pointed out that the first report of a transgenic nematode was in 1988 (Spieth *et al.*, *Dev. Biol.* **130**:285-293; see **Exhibit A** of the Response to the Second Action), the first report of a transgenic mouse was in 1980 (Gordon *et al.*, *Proc. Natl. Acad. Sci. USA* **77**:7380-7384; see **Exhibit B** of the Response to the Second Action), the first report of a transgenic rat was in 1990 (Mullins *et al.*, *Nature* **344**:541-544; see **Exhibit C** of the Response to the Second Action), the first report of a transgenic rabbit was in 1985 (Hammer *et al.*, *Nature* **315**:680-683; see **Exhibit D** of the Response to the Second Action), a report of the production of human interleukin-2 in the milk of transgenic rabbits was published in 1990 (Bühler *et al.*, *Bio/Technology* **8**:140-143; see **Exhibit E** of the Response to the Second Action), the first reports of transgenic guinea pigs were in 2000 (Suzuki *et al.*, *Gene Ther.* **7**:1046-1054, and Yagi *et al.*, *JARO* **1**:315-325; see **Exhibit F** of the Response to the Second Action), a report of the production of human growth hormone in the milk of transgenic guinea pigs was also published in 2000 (Hens *et al.*, *Biochim. Biophys. Acta* **1523**:161-171; see **Exhibit G** of the Response to the Second Action), the first report of a transgenic pig was in 1985 (see **Exhibit D** of the Response to the Second Action), a report of the production of a heterologous milk protein in the milk of transgenic pigs was published in 1991 (Wall *et al.*, *Proc. Natl. Acad. Sci. USA* **88**:1696-1700; see **Exhibit H** of the Response to the Second Action), the first reports of transgenic chickens were in 1987 (Salter *et al.*, *Virology* **157**:236-240; see **Exhibit I** of the Response to the Second Action) and 1989 (Bosselman *et al.*, *J. Virol.* **63**:2680-2689; see **Exhibit J** of the Response to the Second Action), the first reports of transgenic goats were in 1991 (Ebert *et al.*, *Bio/Technology* **9**:835-838, and Denman *et al.*, *Bio/Technology* **9**:839-843; see **Exhibit K** of the Response to the Second Action), and the first report of a transgenic monkey (rhesus monkey) was in January of 2001 (Chan *et al.*, *Science* **291**:309-312; see **Exhibit L** of the Response to the Second Action), the first report of a transgenic cow (raised by the Examiner on page 4 of the Second Action) was in 1991 (Krimpenfort *et al.*, *Bio/Technology* **9**:844-847; see **Exhibit M** of the Response to the Second Action), the first report of a transgenic sheep (another example of a transgenic mammal) was in 1988 (Simons *et al.*, *Bio/Technology* **6**:179-183; see **Exhibit N** of the Response to the Second Action),

and a report of the production of human anti-hemophilic factor IX in the milk of transgenic sheep was published in 1989 (Clark *et al.*, *Bio/Technology* 7:487-492; see **Exhibit O** of the Response to the Second Action). Applicants submit that given the hundreds of reports of transgenic animals, of which the reports listed above are only the **first** examples, there can be no doubt that the **making** and **using** of transgenic animals is clearly enabled to those of skill in the art, which is all that is required to meet the enablement requirement under 35 U.S.C. § 112, first paragraph ("**make** and **use**").

The Examiner admits that "numerous transgenic animals have been made to date", but states that "the experimental usefulness of the animals generated is often a problem", and that "(t)he primary reason for this is that the phenotype remains highly unpredictable" (the Action at page 5). Applicants respectfully point out whether or not any particular non-human transgenic animal is more or less useful in any particular specific application has **no bearing whatsoever** on whether a claim meets the enablement requirement under 35 U.S.C. § 112, first paragraph. **All** that is required in order for claim 7 to comply with the enablement requirement of 35 U.S.C. § 112, first paragraph, is that the skilled artisan be able to "**make**" and "**use**" non-human transgenic animals. The Examiner states that "(f)actors as hard-to-control (*sic*) as the genetic background of the animal can mean success or failure in obtaining the **desired** expression that leads to the **expected** phenotypic outcome" (the Action at page 5, emphasis added). There is **no** such qualitative requirement **anywhere** within 35 U.S.C. § 112, first paragraph, and **no** holding from either the Federal Circuit or the Supreme Court, that would require a particular transgene to have a "desired" expression level or an "expected" phenotypic outcome in order to comply with 35 U.S.C. § 112, first paragraph. Furthermore, the Manual of Patent Examining Procedure clearly states in Section 2164 that "to comply with 35 U.S.C. § 112, first paragraph, it is not necessary to 'enable one of ordinary skill in the art to make and use a perfected, commercially viable embodiment absent a claim limitation to that effect'", citing *CFMT, Inc. v. Yieldup Int'l Corp.*, 68 USPQ2d 1940, 1944 (Fed. Cir. 2003). Regarding non-human transgenic animals, claim 7 contains no specific "claim limitation to that effect". Thus, all that is required in order to satisfy the enablement requirement under 35 U.S.C. § 112, first paragraph, is that the skilled artisan be able to "make" and "use" **any** non-human transgenic animal, not "make" and "use" the **perfect** non-human transgenic animal, or any **specific** non-human transgenic animal. **Any** detectable level of expression of a transgene, for example SEQ ID NO:1, is all that is required. As the skilled artisan is clearly able to "make" and "use" a variety of different species of transgenic animals, claim 7 is therefore enabled as

it is supported by a specification that provides sufficient description to enable the skilled person to make and use the invention as claimed.

The Examiner states that "(r)egarding the instant Application, in view of the lack of guidance provided by the specification for identifying and isolating embryonic cells which can contribute to the germ line of any non-human mammal other than the mouse, such as dogs or cows, the skilled artisan would not have had a reasonable expectation of success in generating any and all non-human transgenic animals using ES cell technology" (the Action at page 6). Applicants respectfully point out that "ES cell technology" is only **one** method of generating transgenic non-human animals taught in the specification as originally filed. As clearly set forth in the specification as originally filed at page 17, lines 11-24:

> Any technique known in the art may be used to introduce a NHP transgene into animals to produce the founder lines of transgenic animals. Such techniques include, but are not limited to pronuclear microinjection (Hoppe, P.C. and Wagner, T.E., 1989, U.S. Pat. No. 4,873,191); retrovirus mediated gene transfer into germ lines (Van der Putten *et al.*, 1985, Proc. Natl. Acad. Sci., USA *82*:6148-6152); gene targeting in embryonic stem cells (Thompson *et al.*, 1989, Cell *56*:313-321); electroporation of embryos (Lo, 1983, Mol Cell. Biol. *3*:1803-1814); and sperm-mediated gene transfer (Lavitrano *et al.*, 1989, Cell *57*:717-723); *etc.* For a review of such techniques, see Gordon, 1989, Transgenic Animals, Intl. Rev. Cytol. *115*:171-229, which is incorporated by reference herein in its entirety.

The specification clearly teaches that **any** technique known in the art can be used to produce non-human transgenic animals, not just "ES cell technology". In fact, U.S. Patent No. 4,873,191, which issued on October 10, 1989 and was referenced in the specification as originally filed (as detailed in the above quote), enables the generation of **any** transgenic mammal utilizing pronuclear microinjection, and each of the referenced techniques have been successfully used by skilled artisans to produce a variety of non-human transgenic animals. Therefore, as the specification as originally filed clearly enables the skilled artisan to "make" and "use" non-human transgenic animals, claim 7 meets the enablement requirement under 35 U.S.C. § 112, first paragraph.

In the context of gene therapy, Applicants pointed out in the Response to the Second Action that there are a number of reports in the literature, prior to the filing date of the present application, concerning a variety of gene therapy vectors and successful gene therapy regimens. Furthermore, in the Second Action, at page 5, the Examiner herself admits that gene therapy can and has been practiced by the skilled artisan ("since 1990, about 3500 patients have been treated via gene therapy"

and "some evidence of gene transfer has been seen"). Applicants submit that given the numerous reports of gene therapy protocols and vectors, not to mention reports of successful gene therapy regimens, there can be no doubt that the **making** and **using** of gene therapy vectors is clearly enabled to those of skill in the art, which Applicants reiterate is all that is required to meet the enablement requirement under 35 U.S.C. § 112, first paragraph ("**make** and **use**").

However, the Examiner states that "successes in the gene therapy art have been limited and very specific", that "design of the vector, the method of targeting, and the host responses al remain critical factors in designing a successfully (*sic*) gene therapy protocol", and therefore "gene therapy remains unpredictable" (the Action bridging pages 6 and 7). Applicants once again respectfully point out that whether or not any particular gene therapy vector or protocol is more or less successful in any particular specific gene therapy application has **no bearing whatsoever** on whether a claim meets the enablement requirement under 35 U.S.C. § 112, first paragraph. It appears that the Examiner seems to believe that claim 7 is not enabled for gene therapy because gene therapy does not always produce a specific therapeutic benefit. Applicants point out once again that there is **no** such qualitative requirement **anywhere** within 35 U.S.C. § 112, first paragraph, and **no** holding from either the Federal Circuit or the Supreme Court, that would require a particular gene therapy vector or protocol to produce a specific therapeutic benefit in order to comply with 35 U.S.C. § 112, first paragraph. As noted above, the Manual of Patent Examining Procedure clearly states in Section 2164 that "to comply with 35 U.S.C. § 112, first paragraph, it is not necessary to 'enable one of ordinary skill in the art to make and use a perfected, commercially viable embodiment absent a claim limitation to that effect'", citing *CFMT, Inc. v. Yieldup Int'l Corp.*, 68 USPQ2d 1940, 1944 (Fed. Cir. 2003). With regard to gene therapy, claim 7 contains no specific "claim limitation to that effect". Thus, all that is required in order to satisfy the enablement requirement under 35 U.S.C. § 112, first paragraph, is that the skilled artisan be able to "make" and "use" **any** gene therapy vector or protocol, not "make" and "use" the **perfect** gene therapy vector or protocol, or any **specific** gene therapy vector or protocol. As the skilled artisan is clearly able to "make" a variety of different gene therapy vectors for "use" in a variety of gene therapy protocols or regimens, claim 7 is therefore enabled as it is supported by a specification that provides sufficient description to enable the skilled person to make and use the invention as claimed.

Furthermore, with regard to a requirement that the host cells of claim 7 be nearly always

effective in gene therapy, such an enablement standard conflicts with established patent law. As discussed in *In re Brana,* 34 USPQ2d 1436 (Fed. Cir. 1995; "*Brana*"), the Federal Circuit admonished the USPTO for confusing "the requirements under the law for obtaining a patent with the requirements for obtaining government approval to market a particular drug for human consumption". *Brana* at 1442. The Federal Circuit went on to state:

> At issue in this case is an important question of the legal constraints on patent office examination practice and policy. The question is, with regard to pharmaceutical inventions, what must the applicant provide regarding the practical utility or usefulness of the invention for which patent protection is sought. This is not a new issue; it is one which we would have thought had been settled by case law years ago.

Brana at 1439, emphasis added. The Federal Circuit concluded:

> FDA approval, however, is not a prerequisite for finding a compound useful within the meaning of the patent laws. Usefulness in patent law, and in particular in the context of pharmaceutical inventions, necessarily includes the expectation of further research and development. The stage at which an invention in this field becomes useful is well before it is ready to be administered to humans. Were we to require Phase II testing in order to prove utility, the associated costs would prevent many companies from obtaining patent protection on promising new inventions, thereby eliminating an incentive to pursue, through research and development, potential cures in many crucial areas such as the treatment of cancer.

Brana at 1442-1443, citations omitted, emphasis added. Thus, based on the holding in *Brana*, claim 7 clearly meets the enablement requirement under 35 U.S.C. § 112, first paragraph.

The Examiner maintains that the present invention could not be practiced without "undue experimentation" (the Action at page 7). Applicants pointed out in the Response to the Second Action that in assessing the question of whether undue experimentation would be required in order to practice the claimed invention, the key term is "undue", not "experimentation" (*In re Angstadt and Griffin*, 190 USPQ 214 (CCPA 1976)). The large number of reports in the literature on a variety of transgenic animals, as well as gene therapy vectors and regimens, strongly argues against such uses requiring "undue experimentation". In *In re Wands* (8 USPQ2d 1400 (Fed. Cir. 1988); "*Wands*"), the United States Patent and Trademark Office ("the USPTO") took the position that the applicant failed to demonstrate that the disclosed biological processes of immunization and antibody selection could reproducibly result in a useful biological product (antibodies from hybridomas) within the scope of the claims. In its decision overturning the USPTO's rejection, the Federal Circuit found that Wands'

demonstration of success in four out of nine cell lines screened was sufficient to support a conclusion of enablement. The court emphasized that the need for some experimentation requiring, *e.g.*, production of the biological material followed by routine screening, was not a basis for a finding of non-enablement, stating:

> Disclosure in application for the immunoassay method patent does not fail to meet enablement requirement of 35 USC 112 by requiring 'undue experimentation', even though production of monoclonal antibodies necessary to practice invention first requires production and screening of numerous antibody producing cells or 'hybridomas', since practitioners of art are prepared to screen negative hybridomas in order to find those that produce desired antibodies, since in monoclonal antibody art one 'experiment' is not simply screening of one hybridoma but rather is entire attempt to make desired antibody, and since record indicates that amount of effort needed to obtain desired antibodies is not excessive, in view of Applicants' success in each attempt to produce antibody that satisfied all claim limitations.

Wands at 1400. Thus, the need for some experimentation does not render the claimed invention unpatentable under 35 U.S.C. § 112, first paragraph. Indeed, a considerable amount of experimentation may be permissible if such experimentation is routinely practiced in the art. *In re Angstadt and Griffin, supra*; *Amgen, Inc. v. Chugai Pharmaceutical Co., Ltd.*, 18 USPQ2d 1016 (Fed. Cir. 1991).

Therefore, based on the overwhelming evidence of record that it is well-known to skilled artisan how to make and use a variety of species of transgenic animals, as well as a variety of gene therapy vectors and regimens, the 35 U.S.C. § 112, first paragraph, rejection is improper:

> As a matter of patent office practice, then, a specification disclosure which contains a teaching of the manner and process of making and using the invention in terms which correspond in scope to those used in describing and defining the subject matter sought to be patented must be taken as in compliance with the enabling requirement of the first paragraph of § 112 unless there is reason to doubt the objective truth of the statements contained therein which must be relied on for enabling support.

In re Marzocchi, 169 USPQ 367, 369 (CCPA 1971), emphasis as in original. Applicants respectfully point out that, as a matter of law, it is well settled that a patent need not disclose what is well-known in the art. *In re Wands, supra*. In fact, it is preferable that what is well-known in the art be omitted from the disclosure. *Hybritech, Inc. v. Monoclonal Antibodies, Inc.*, 231 USPQ 81 (Fed. Cir. 1986). Therefore, the full breadth of claim 7 is clearly enabled.

Finally, Applicants respectfully point out that the requirements set forth in the Action for

compliance with the enablement requirement of 35 U.S.C. § 112, first paragraph, do not comply with the requirements set forth by the United States Patent and Trademark Office ("the USPTO") itself for compliance with 35 U.S.C. § 112, first paragraph. This is underscored by numerous patents that have been issued over the years, which were filed prior to the priority date of the present application, that specifically claim "a host cell". As just three examples of such issued U.S. Patents, the Examiner is invited to review U.S. Patent Nos. 6,492,150 (filed on July 3, 1996), 6,498,021 (filed on May 31, 2000), and 6,500,635 (filed November 28, 1994; **Exhibits A-C**; copies of issued U.S. Patents not provided pursuant to requests from the USPTO). As issued U.S. Patents are presumed to meet all of the requirements for patentability, including 35 U.S.C. § 112, first paragraph, Applicants submit that claim 7 must also meet the requirements of 35 U.S.C. § 112, first paragraph. While Applicants understand that each application is examined on its own merits, if it is the Examiner's position that a claim directed to "a host cell" reads "on isolated host cells, *as well as* host cells in the context of a multicellular, transgenic organism and host cells intended for gene therapy", and non-human transgenic animals and gene therapy were not enabled as of September 1, 2000 (the priority date of the present application), since the skilled artisan could not practice non-human transgenic animals or gene therapy without "undue experimentation", Applicants cannot understand how a claim to "a host cell" in these patents filed prior to September 1, 2000 meets the enablement requirement under 35 U.S.C. § 112, first paragraph, while claim 7 in the present application does not. Holding Applicants to a different standard of enablement would be arbitrary and capricious, and, like other clear violations of due process, cannot stand.

For each of the foregoing reasons, as well as the reasons set forth in the Response to the Second Action, Applicants respectfully request that the rejection of claim 7 under 35 U.S.C. § 112, first paragraph, be withdrawn.

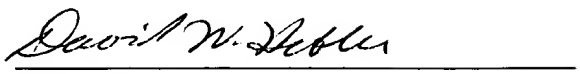
III. Conclusion

The present document is a full and complete response to the Action. In conclusion, Applicants submit that, in light of the foregoing remarks, the present case is in condition for allowance, and such favorable action is respectfully requested. Should Examiner Wegert have any questions or comments, or believe that certain amendments of the claims might serve to improve their clarity, a telephone call

to the undersigned Applicants' representative is earnestly solicited.

Respectfully submitted,

September 21, 2005
Date



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